SUPPORT FOR THE AMENDMENTS

Applicants have amended 10, 14, 20, 24, 37, 42, and 46 in order that Claims 11, 15, 21, 25, 38, 43, and 47 are properly dependent. Applicants have also added new Claims 54 and 55. Support for new Claims 54 and 55 can be found in Claims 13-16 and 18-21.

No new matter has been added. Claims 8-48, 54, and 55 are pending in the present application.

REMARKS/ARGUMENTS

Present Claims 8-11 relate to effervescent pharmaceutical compositions comprising levodopa methyl ester and an acid-base couple, wherein administering a single oral dose of said composition to a human provides to said human a maximum plasma concentration of levodopa at about 0.3 hours (T_{max}) after said administering.

Present Claims 12-16 and 54 relate to pharmaceutical compositions comprising levodopa methyl ester (LDME) and an acid-base couple, wherein administering a single oral dose of said composition to a human provides to said human a mean maximum plasma concentration of levodopa (C_{max}/dose) of about 9.6 ng/mL/[mg LDME] after said administering.

Present Claims 17-21 and 55 relate to pharmaceutical compositions comprising levodopa methyl ester (LDME) and an acid-base couple, wherein administering a single oral dose of said composition to a human provides to said human an area under the curve of levodopa in plasma from 0 to 1 hour (AUC_{1h}/dose) of about 5.3 ng·hr/mL/[mg LDME] after said administering.

Present Claims 22-25 relate to pharmaceutical compositions comprising levodopa methyl ester and an acid-base couple, wherein administering a single oral dose of said

composition to a human provides to said human a ratio of about 2.7 of mean plasma concentration of levodopa at 15 minutes after said administering compared to 60 minutes after said administering.

Present Claims 26-34 relate to pharmaceutical compositions comprising levodopa methyl ester (LDME) and an acid-base couple, wherein administering a single oral dose of said composition to a human provides to said human a mean plasma concentration (C_p) of levodopa of about 8.8 ng/mL/[mg LDME] 15 minutes after said administering.

Thus, the present claims are drawn to pharmaceutical compositions comprising levodopa methyl ester (LDME) and an acid-base couple, wherein administering a single oral dose of said composition to a human provides:

- a maximum plasma concentration of levodopa at about 0.3 hours (T_{max}) after said administering (claim 8);
- a mean maximum plasma concentration of levodopa (C_{max}/dose) of about 9.6 ng/mL/[mg LDME] after said administering (claim 12);
- an area under the curve of levodopa in plasma from 0 to 1 hour (AUC_{1h}/dose) of about 5.3 ng·hr/mL/[mg LDME] after said administering (claim 17);
- a ratio of about 2.7 of mean plasma concentration of levodopa at 15 minutes after said administering compared to 60 minutes after said administering(claim 22);
- a mean plasma concentration (C_p) of levodopa of about 8.8 ng/mL/[mg LDME] 15 minutes after said administering (claim 26).

and wherein:

- said acid-base couple is sodium glycine carbonate -fumaric acid (claims 9, 13, 19, 23, and 32);

- said composition further comprises carbidopa monohydrate (claims 10, 14, 20, 24, and 33); and
- the weight ratio of levodopa methyl ester to carbidopa monohydrate to sodium glycine carbonate to fumaric acid is about 1.0:0.09:1.7:1.1, respectively (claims 11, 15, 21, 25, and 34).

In particular the composition of the present invention:

- because of its light effervescence and rapid disintegration is a *fast dissolving* formulation
- after single oral dose administration show a more *rapid absorption* and an active ingredient higher exposure during the *first hours after administration* in comparison to the standard commercial formulation (see paragraph [0116]).

In fact all the pharmacokinetics parameters detailed in the independent claims relate to the fast oral absorption profile of levodopa and carbidopa released from effervescent tablets according to the present invention.

The rejection of Claims 8-34 under 35 U.S.C. §103(a) over Chiesi (US 4,826,875) in view of Barry et al (US 5,055,306) is respectfully traversed. Applicants respectfully submit that the combined disclosures of Chiesi and Barry et al fail to disclose, explicitly or implicitly, or suggest all the limitations of the claims and, thus, fails to render the claimed invention obvious. For the Examiner's reference, Applicants submit the following detailed summary of the deficiencies in Chiesi and Barry et al.

In contrast to the present invention, Barry et al discloses "a granular ***sustained-release*** formulation of a pharmacologically active substance presented in the form of a tablet, said tablet comprising sufficient granules to provide a predetermined dose or number of doses of

the pharmacologically active substance and effervescent or water-dispersible ingredients, each of *said granules* preferably having a diameter of between 0.5 and 2.5 mm and comprising:

a) *a core* comprising one or more pharmacologically active substances and preferably one or more excipients; and

b) *a coating covering substantially the whole surface of the core* and comprising 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative, the weight of the coating being from 2 to 25% of the weight of the core." (see column 3 lines 37 to 53, emphasis added)

Moreover Barry et al states: "the formulations of this invention are thus presented in the form of tablets which disintegrate into *sustained-release -granules* upon coming into contact with an aqueous liquid." (see column 4 lines 6 to 9, emphasis added)

Therefore, even if Barry et al describes effervescent tablets comprising, in the effervescent couple, maleic acid, fumaric acid or its monosodium salt and glycine sodium carbonate, these formulations are applied to ***sustained-release granules*** comprising a core, including the active ingredient, coated by "a water insoluble but water swellable acrylic polymer and a water soluble hydroxylated cellulose derivative" (see column 6, line 34 to 35), to provide a sustained release over a period of 12 to 24 hours (see column 5, line 64 to column 6, line 9). In contrast, the composition of the present invention is a typified by the fast dissolution and rapid absorption of the active ingredient constituted by the combination levodopa methyl ester + carbidopa (see Example 19).

Moreover, Barry et al suffers an even more fatal flaw with respect to the claimed invention. At no point do Barry et al disclose or suggest the required claim element of levodopa methyl ester. Barry et al only generally discloses among the pharmacologically active substances appearing in column 7, lines 3-46 that the active ingredient in their sustained-release formulations include:

- anti-hypertensives e.g. methyldopa, levodopa and prazosin (see column 7, lines 12-13); and
- antiparkinsonism drugs e.g. benzhexol, levodopa) (see column 7, lines 28-29).

However, at no point is levodopa methyl ester, or even carbidopa disclosed by Barry et al.

Chiesi report that levodopa methyl ester can be used as active principle of pharmaceutical compositions with surprising therapeutic effects in all kinds of parkinsonism and in the neurologic syndromes related to it. In particular, Chiesi describes pharmaceutical compositions for oral or sublingual administration in solid (i.e. tablets) or liquid form. The compositions described, which may contain levodopa methyl ester in combination with benserazide, carbidopa or deprenyl, do not contain an effervescent couple.

Even if Barry et al were combined with Chiesi, it would not be possible to reach the same results of the present invention, since the coating on the core disclosed by Barry et al containing the active ingredient would lead to a controlled/retarded release of the active ingredient.

In the present invention the active ingredients LDME and carbidopa are not present in the form of polymer coated sustained release granules but the two substances are mixed as such with the acid-base effervescent couple, the optional excipients and directly tabletted. Such a formulation allows to reach a maximum plasma concentration in a shorter time after the administration than in Chiesi, while in Barry et al there is no suggestion to prepare rapid soluble /rapid absorption formulations because the active ingredient is coated by polymers.

Further, it would not be possible, among components of the effervescent couple cited in Barry et al, to select the components described in the present invention (e.g., glycine, sodium carbonate and fumaric acid) in order to obtain effervescent tablets having fast dissolution and rapid absorption in the first hour after administration. This is shown by the following pharmacokinetics parameters:

- T_{max} (i.e., time to maximum concentration)
- C_{max}/dose (i.e., mean maximum plasma concentration /dose [mg LDME])
- AUC_{1h}/dose (i.e., area under the curve of levodopa in plasma from 0 to 1 hour/dose [mg LDME])
- ratio of mean plasma concentration of levodopa at 15 minutes after administration compared to 60 minutes after said administration,
- mean plasma concentration of levodopa (C_p) 15 minutes after said administration.

Further, the values of these parameters, claimed for the formulation of the present invention (See Example 19, Table 8 and claims 8, 12, 17, 22, 26) as compared with the calculated values based on the data reported in Example 8, Table 1 of Chiesi are as follows:

	Claimed invention	Chiesi (calculated)
T_{max} (claim 8)	About 0.3 h	0.75h
C_{max}/dose (claim 12)	About 9.6 ng/mL/[mg LDME]	6.0 ng/mL/[mg LDME]
AUC_{1h}/dose (claim 17)	about 5.3 ng·hr/mL/[mg LDME]	4.3 ng·hr/mL/[mg LDME]
ratio of mean plasma concentration of levodopa at 15 minutes after administration compared to 60 minutes after said administration (claim 22)	About 2.7	0.83
mean plasma concentration of levodopa (C_p) 15 minutes after said administration (claim 26)	About 8.8 ng/mL/[mg LDME]	3.5 ng/mL /[mg LDME]

In the Office Action dated June 15, 2007, the position is taken that "Chiesi discloses single oral dosage data of levodopa methyl ester (LDME) plasmatic levels at different times after administration" (see page 2 of the Office Action mailed June 15, 2007); however, the it

is incorrectly asserted that the maximum concentration peak is reached "at 0.31 minutes from the administration." (see page 2 of the Office Action mailed June 15, 2007)

In fact, according to the disclosure of Chiesi "the absorption of LDME was very rapid reaching the maximum concentration peak at ***40-45 minutes*** from administration" (see column 5, lines 30-32). Further, in Table I (column 5), Chiesi show that the maximum plasmatic levels of levodopa are obtained at about 45-80 minutes (i.e., 0.75-1.3 hr) after the administration of LDME. Such a result is in direct contrast to the present invention where the maximum plasma concentration of levodopa is achieved in about 0.3 hours (Tmax: see Table 7), corresponding to about ***18-20 minutes***. Accordingly, the effervescent composition of the present invention provides for a shorter time to levodopa maximum concentration as compared to the composition of Chiesi.

It should be further noted that the data on the rapid absorption of levodopa, shown in Table 1 of Chiesi, refer to the composition of Example 1 that is a "ready solution administrable by drops" (see column 5, lines 18-23). This formulation requires the presence of preservatives to be adequately stored. In fact, in the composition of Example 1 of Chiesi preservatives such as methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are included, but also an antioxidant such as metabisulfite may be optionally added (Column 4, lines 1-3).

However, to avoid side effects and allergic phenomena in the patients, the use of preservatives in pharmaceutical preparations is not advisable. In the present invention it has been observed that by using the particular effervescent couple fumaric acid and glycine sodium carbonate, preservative free solid effervescent formulations of LDME, showing faster oral absorption than ready solution formulation, are obtained.

Therefore, it can be observed that the formulations of effervescent tablets for the present invention showed a more rapid absorption and an active ingredient higher exposure

during the first hours after administration with respect to the formulation of the Chiesi. The skilled artisan would not be motivated to modify Chiesi or obtain these results when combining this disclosure with Barry et al. This is particularly true when considering that the formulation disclosed by Barry et al is a suspended-release formulation.

Accordingly, Applicants submit that there is no suggestion in the cited prior art to select the particular acid-base effervescent couple (i.e., fumaric acid and glycine sodium carbonate) of the present invention to obtain a faster dissolving formulation of LDME-carbidopa provided with a more rapid absorption of levodopa and higher exposure during the first hours after a single oral dose administration that those provided in the disclosure of Chiesi (see Table above).

In view of the foregoing, Applicants submit that the presently claimed invention is not obvious in view of the combined disclosures of Chiesi and Barry et al. As such, withdrawal of this ground of rejection is requested.

In any event, Applicants have added new Claims 54 and 55. Applicants respectfully submit that there is nothing in either of the cited references taken alone or in combination which would make Claims 54 and 55 obvious. Accordingly, these claims should be allowed.

The obviousness type-double patenting rejection of Claims 8, 10, and 11 over Claim 1 of U.S. 6,284,272 has been obviated by submission of an executed Terminal Disclaimer. Accordingly, Applicants believe that this ground of rejection is no longer at issue and should be withdrawn. Acknowledgement to this effect is requested.

Finally, with respect to the withdrawn method claims, the Examiner is reminded of rejoinder as discussed in MPEP §821.04. Applicants note that should the examined product claims (i.e., Claims 8-34) be found allowable, withdrawn process claims (minimally Claims

35-48) should be rejoined and examined as these claims contain all the limitations of the examined product claims. An action to this effect is requested.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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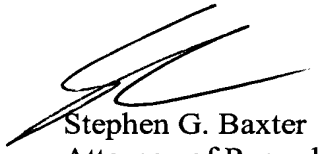

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